MEDICAL BREAST TRAINING PROGRAM
2022 – BLENDED ONLINE & LIVESTREAM

In collaboration with

Jointly sponsored by
SUPPLEMENTAL BREAST IMAGING
BREAST CANCER SCREENING

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Associate Professor of Radiology
DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Hologic Inc, Research grant to Mayo Clinic

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

_All relevant financial relationships have been mitigated._
LEARNING OBJECTIVES

• Articulate the evolving needs for supplemental imaging including:
  • False negatives in breast cancer imaging
  • The importance of breast density and legal implications

• Describe and compare the different anatomic and functional modalities for supplemental imaging including:
  • Digital breast tomosyntheses (DBT)
  • Screening breast ultrasound (US)
  • Contrast-enhanced mammography (CEM)
  • Molecular breast imaging (MBI),
  • Full sequence magnetic resonance imaging (MRI) and abbreviated MRI (AB-MRI)
MAMMOGRAPHY REDUCES BREAST CANCER MORTALITY

• Only imaging modality proven to reduce breast cancer mortality
  • Reduces breast cancer specific mortality by ~28% among women invited for screening mammography

• Mammographic performance is dependent on breast density

MAMMOGRAPHY
BREAST DENSITY

• The amount of fibroglandular tissue relative to fat
• Determined either visually or quantitatively on mammography

IS MAMMOGRAPHY ENOUGH?

- Sensitivity of mammography decreases with increasing breast density
  - 73% in extremely dense
  - 90% in fatty breasts
  - As low as 30-50% in BRCA patients

- Interval cancers arise due to limited sensitivity in women with dense breasts

- Limited specificity 25-45% PPV for biopsy recommendation

- Limitations of mammography highlight the need for more effective screening strategies, especially in patients with dense breasts and increased risk


## BREAST DENSITY INCREASES CANCER RISK

<table>
<thead>
<tr>
<th>Density</th>
<th>Relative risk of breast cancer</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost entirely fatty</td>
<td>0.5</td>
<td>13%</td>
</tr>
<tr>
<td>Scattered densities</td>
<td>1 (reference group)</td>
<td>43%</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td>1.5 - 1.6</td>
<td>36%</td>
</tr>
<tr>
<td>Extremely dense</td>
<td>1.8 - 2.0</td>
<td>7%</td>
</tr>
</tbody>
</table>

PATIENTS AND PROVIDERS SHOULD BE INFORMED OF BREAST DENSITY

• Women with dense breasts experience:
  • Increased false-positives mammographic findings
  • Reduced cancer detection rate
  • More interval cancers
  • Less improvement in breast cancer mortality

• Patients and providers must be aware of breast density and how density can limit ability to detect breast cancer

MAMMOGRAPHY
PROLIFERATION OF STATE AND NATIONAL BREAST DENSITY REPORTING LAWS

CONGRESS DIRECTS FDA TO ESTABLISH FEDERAL BREAST DENSITY INFORM STANDARD

Agency will develop reporting language for minimum amount of information to be provided about a patient’s individual fibroglandular density and associated breast cancer risk

https://www.areyoudense.org

Accessed March 2022
IMPACT OF STATE BREAST DENSITY REPORTING LAWS

• Women want to know their breast tissue density (90%, national survey, n=1500)
• Women can obtain their density information from: PCPs, imaging reports, or mammography patient lay letter (particularly if in states requiring such letters)
• State breast density reporting laws:
  • Increase the likelihood that women learn of their breast density
  • Promote healthcare providers speaking with women about supplemental screening
  • Women from states with laws in place longer were more likely to know their own density type and, for those with dense breasts, were more likely to say their health care provider talked to them about additional screening

Cappello NM, et al. JACR 2019; 16(2):139-146
SUPPLEMENTAL SCREENING OPTIONS
BREAST DENSITY: REVIEW OF MODALITIES AND LITERATURE

• Women with increased breast density may benefit from supplemental breast cancer screening, such as with:
  • Digital breast tomosynthesis (DBT)
  • Ultrasound (US)
  • Molecular breast imaging (MBI)
  • Magnetic resonance imaging (MRI)
  • Contrast-enhanced mammography (CEM)
SUPPLEMENTAL SCREENING FLOW CHART

Genetic testing by age 30 years; disease-causing mutation identified

--- YES ---

Annual MRI only ages 25-29 years; for patients older than 30 years old, perform annual MRI as a supplement to digital mammography or DBT

--- NO ---

PHBC and diagnosis by age 50 years or dense breasts OR history of LCIS or ADH

--- NO ---

At least 40 years old

--- NO ---

Begin digital mammography or DBT at age 40 years (consider starting annual mammography 10 years before age of close relative(s) at time of diagnosis but not before age 30 years)

--- YES ---

Risk assessment shows lifetime risk >20-25%

--- YES ---

Perform annual digital mammography or DBT as well as annual MRI

--- NO ---

History of chest radiation therapy by age 30 years at least 8 years prior OR

--- NO ---

Assess breast density (visually or quantitatively). Are the breasts dense?

--- NO ---

Perform annual digital mammography or DBT; reassess risks every year

--- YES ---

Perform annual digital mammography or DBT; consider adding screening MRI (preferred) or screening US especially if breasts are extremely dense

--- NO ---

Perform baseline digital mammography examination or DBT

--- YES ---

Assess breast density (visually or quantitatively). Are the breasts dense?

--- NO ---

Perform annual digital mammography or DBT; reassess risks every year

--- YES ---

Reassess risks and density every year

### SUPPLEMENTAL SCREENING OPTIONS

ICDR, RECALL RATES, INTERVAL CANCERS

Summary of comparative impact of supplemental screening beyond 2D mammography for women with dense breasts and surrogate endpoint validation

<table>
<thead>
<tr>
<th>Screening modality</th>
<th>No. of patients</th>
<th>Incremental CDRa</th>
<th>Incremental invasive CDRa</th>
<th>Node-negative invasive cancers, %b</th>
<th>Incremental recall ratea</th>
<th>Reduced interval cancers</th>
<th>Reduced late-stage disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBT</td>
<td>103,245c</td>
<td>1.7c</td>
<td>1.4d</td>
<td>Not evaluated</td>
<td>-20c</td>
<td>No</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>US</td>
<td>452,743g</td>
<td>2.0-2.7g</td>
<td>1.8-2.3g</td>
<td>88.6 (635/717)</td>
<td>76-106</td>
<td>Yes</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>MBIf</td>
<td>4277</td>
<td>8.1</td>
<td>6.2</td>
<td>85 (23/27)</td>
<td>67</td>
<td>Not yet evaluated</td>
<td>Not yet evaluated</td>
</tr>
<tr>
<td>MRI</td>
<td>9256g</td>
<td>16.0</td>
<td>12.1</td>
<td>88 (99/112)</td>
<td>104</td>
<td>Yes</td>
<td>Not yet evaluated</td>
</tr>
<tr>
<td>MRI after DBT</td>
<td>1444i</td>
<td>9.7</td>
<td>6.9</td>
<td>94 (16/17)</td>
<td>215</td>
<td>Not yet evaluated</td>
<td>Yesb</td>
</tr>
<tr>
<td>CEMj</td>
<td>1311i</td>
<td>10.7</td>
<td>8.4</td>
<td>75 (6/8)</td>
<td>150j</td>
<td>Not yet evaluated</td>
<td>Not yet evaluated</td>
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Note: CDR = cancer detection rate, DBT = digital breast tomosynthesis, US = ultrasound, MBI = molecular breast imaging, CEM = contrast-enhanced mammography.

- aPer 1000 women screened.
- bData in parentheses are number of invasive breast cancers staged that were node negative/total number of invasive breast cancers seen only on that modality.
- cThe CDR of DBT was 682 cancers detected among 103,245 women (6.61 cancers detected per 1000 women screened) across the four studies presented in Table 1, versus 876 cancers detected among 176,986 women (4.95 cancers detected per 1000 women screened) for 2D mammography, for a difference of 1.7 cancers detected per 1000 women screened; there were 12, 280 recalls per 113,986 DBT examinations (10.8%) versus 23,727 recalls per 185,763 2D examinations (12.8%), for a difference of 2.0% or 20 recalls per 1000 examinations.
- dData are from [43] only; incremental invasive DCR data were not reported in the other studies.
- eSummary of comparative impact of supplemental screening beyond 2D mammography for women with dense breasts and surrogate endpoint validation.
- fData from three series [65,66,100] limited to women with dense breasts on prior or current mammogram.
- gData from the three of the series [54,81,82] summarized in Table 2. In Kuhl et al. [81], the incremental CDR for prevalence screening versus incidence screening was 22.6 cancers per 1000 women screened versus 6.9 cancers per 1000 women screened, respectively. Other findings are for prevalence screening.
- hReduced late-stage disease has been shown only for women with known pathogenic BRCA1 or BRCA2 mutations screened using MRI [74].
- iPrevalence screening with abbreviated MRI compared with tomosynthesis [87], as described in Table 2.
- jData are from two series [95,96]. Cancer findings are shown for the 700 women with dense breasts in the series evaluated by Sung et al. [96], whereas recall rates included false-positive and true-positive recalls for all 904 women because results were not distinguished for the subset of women with dense breasts.
DIGITAL BREAST TOMOSYNTHESIS
SUPPLEMENTAL SCREENING

• Technique: Multiple, angled, low-dose projection images are acquired and reconstructed into thin (typically 1mm) slices

• Impact: DBT reduces false-positive recalls due to summation artifact [32] and also because of its better depiction of multiplicity and bilaterality of circumscribed masses (allowing benign assessment [40])

• DBT associated with
  • Increased cancer detection rate (CDR, +1.2- 2.7/1000) compared to conventional 2D mammography
  • 2% absolute reduction in recall rate (RR, relative 15–17%)
  • Increased CDR and decreased RR for both dense and non-dense tissue
**DIGITAL BREAST TOMOSYNTHESIS**  
**SUPPLEMENTAL SCREENING**

### Recall rate

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>CDR per 1000 screening examinations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondense</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>79 (6955/89,171)</td>
<td>5.1 (455/89,171)</td>
</tr>
<tr>
<td>DM</td>
<td>90 (12,845/146,910)</td>
<td>4.2 (610/146,901)</td>
</tr>
<tr>
<td>Difference</td>
<td>-12 &lt;0.001</td>
<td>0.95 &lt;0.001</td>
</tr>
<tr>
<td>Dense</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>109 (9030/84,243)</td>
<td>5.8 (495/84,243)</td>
</tr>
<tr>
<td>DM</td>
<td>127 (16,582/131,996)</td>
<td>4.5 (597/131,996)</td>
</tr>
<tr>
<td>Difference</td>
<td>-18 &lt;0.001</td>
<td>1.4 &lt;0.001</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>110 (7852/72,481)</td>
<td>6.1 (450/72,481)</td>
</tr>
<tr>
<td>DM</td>
<td>128 (41,484/113,290)</td>
<td>4.5 (528/113,290)</td>
</tr>
<tr>
<td>Difference</td>
<td>-18 &lt;0.001</td>
<td>1.6 &lt;0.001</td>
</tr>
<tr>
<td>Extremely dense</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>98 (1178/11,762)</td>
<td>3.9 (45/11,762)</td>
</tr>
<tr>
<td>DM</td>
<td>114 (2098/18,706)</td>
<td>3.8 (69/18,706)</td>
</tr>
<tr>
<td>Difference</td>
<td>-16 &lt;0.001</td>
<td>0.1 0.88</td>
</tr>
</tbody>
</table>

### CDR per 1000 screening examinations

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finding, breast density, and modality</strong></td>
<td>Value</td>
<td>p</td>
<td>Value</td>
<td>p</td>
</tr>
<tr>
<td>Nondense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>8.4 (51/6079)</td>
<td>5.1 (455/89,171)</td>
<td>7.7 (122/15,785)</td>
<td>5.6 (87/15,612)</td>
</tr>
<tr>
<td>DM</td>
<td>5.6 (34/6079)</td>
<td>4.2 (610/146,901)</td>
<td>6.9 (94/15,785)</td>
<td>4.5 (301/66,664)</td>
</tr>
<tr>
<td>Difference</td>
<td>2.8                &lt;0.0001</td>
<td>0.95 &lt;0.001</td>
<td>1.8                 &lt;0.001</td>
<td>1.1                 0.091</td>
</tr>
<tr>
<td>Dense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>66. (8/1215)</td>
<td>5.8 (495/84,243)</td>
<td>12.5 (106/8466)</td>
<td>7.8 (73/9321)</td>
</tr>
<tr>
<td>DM</td>
<td>4.1 (5/1215)</td>
<td>4.5 (597/131,996)</td>
<td>9.7 (82/8466)</td>
<td>5.4 (192/35,309)</td>
</tr>
<tr>
<td>Difference</td>
<td>2.5                0.25</td>
<td>1.4 &lt;0.001</td>
<td>2.8                 &lt;0.001</td>
<td>2.4 &lt;0.0001</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM and DBT</td>
<td>NR</td>
<td>6.1 (450/72,481)</td>
<td>12.5 (83/6645)</td>
<td>NR</td>
</tr>
<tr>
<td>DM</td>
<td>NR</td>
<td>4.5 (526/113,290)</td>
<td>9.6 (84/6645)</td>
<td>NR</td>
</tr>
<tr>
<td>Difference</td>
<td>NR</td>
<td>1.6 &lt;0.001</td>
<td>2.9                 &lt;0.001</td>
<td>NR</td>
</tr>
<tr>
<td>Extremely dense</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>NR</td>
<td>3.9 (45/11,762)</td>
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<td>NR</td>
</tr>
<tr>
<td>DM</td>
<td>NR</td>
<td>3.8 (69/18,706)</td>
<td>9.9 (18/1821)</td>
<td>0.6                  NR</td>
</tr>
<tr>
<td>Difference</td>
<td>NR</td>
<td>0.1 &lt;0.001</td>
<td>2.8                 &lt;0.001</td>
<td>NR</td>
</tr>
</tbody>
</table>

### Summary of studies showing incremental increase in cancer detection and decrease in recall rates after addition of DBT to DM for evaluation of dense and nondense breasts

- **CDR per 1000 screening examinations**
- **Finding, breast density, and modality**
- **Value**
- **p**
- **Difference**

Redrawn from presenter-supplied original; no source supplied.

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SCREENING ULTRASOUND
SUPPLEMENTAL SCREENING

• Technique
  • No ionizing radiation or IV contrast agents
  • Whole-breast US, hand-held US (HHUS) and automated US (AUS)
  • Requires specialized radiologist and technologist training
  • Subject to high inter-user variability

• US as supplemental screening (adding screening US to mammography)
  • Reduces rates of interval cancer rates for women with dense breasts
  • For women with dense breasts, the ICDR was 2.0-2.7 cancers per 1000 screening examinations (using either an AUS or HHUS technique)
  • Detects minimal cancer: 88% cancers are invasive, node negative (80-90%), and small (mean size 7-14mm)
  • US detects some invasive lobular cancers not seen on mammography (15-20% of ILCs seen on US only)
  • In women with dense breasts, US after DBT detects 0.9-2.6 additional cancers / 1000 (HHUS)
SCREENING ULTRASOUND

BARRIERS

• High prevalence of benign cystic lesions results in high rate of false positive findings [60]

• Shortage of trained personnel (for HHUS)

• Large numbers of images (for AUS)

• Artificial intelligence may facilitate interpretation of both HHUS and AUS

• Among women who undergo screening MRI, screening US offers no additional benefit [61]

MOLECULAR BREAST IMAGING
SUPPLEMENTAL SCREENING

• Technique:
  • Established intravenous cardiac nuclear pharmaceutical (Sestamibi)
  • Dedicated breast gamma camera detects 99mTc-sestamibi in mitotically active breast tissue
  • Images function rather than anatomy
  • Not limited by dense breast tissue

• Performance:
  • ICDR of MBI was ~6.9 invasive cancers per 1000 screening examinations
  • Rate of interval cancer detection was 1.3 cancers per 1000 screens

Hruska CB. Molecular breast imaging for screening in dense breasts: state of the art and future directions. AJR 2017; 208:275–283
Brown M, Covington MF. Comparative benefit to risk of molecular breast imaging, 2D full-field digital mammography with and without tomosynthesis, and synthetic mammography with tomosynthesis. Radiol Imaging Cancer 2019; 1:1–7
MAMMOGRAPHICALLY-OCCULT ILC DETECTED BY MBI

Grade III invasive lobular carcinoma, 3.6cm

Slide courtesy of Carrie Hruska, PhD
MOLECULAR BREAST IMAGING

BARRIERS TO USE

• Longer examination time (40 mins)

• Systemic whole-body radiation exposure
  • Effective dose of 2mSv for MBI (0.5 for DM/DBT)
  • 2 mSv is less than the annual background radiation limit (mean, 3.1mSv) and considered low risk for harmful effects
  • Radiation dose is primarily to the colon

• Research needed to validate processing algorithms that can reduce dose and acquisition time [68]
BREAST MRI
SUPPLEMENTAL SCREENING—HIGH RISK

• High risk: defined as lifetime risk of breast cancer ≥20%

• MRI Technique:
  • Most sensitive modality for breast cancer detection
  • Not limited by breast density and is without ionizing radiation.
  • Utilizes gadolinium-based contrast agent to detect differential vascularity and enhancement associated with cancer

• Performance: Data is available for high-risk patients:
  • 16 additional cancers detected by MRI after mammography plus US
  • Detects minimal cancers (avg size 9mm)
  • Reduces interval cancers and late-stage disease
BREAST MRI
SUPPLEMENTAL SCREENING- AVG RISK, DENSE BREASTS

• Trials:
  • ACRIN 6666 trial: MR plus US yielded ICDR of 14.7 cancers per 1000 women
  • Kuhl et al, ICDR 20.3/1000 prevalence and 8.6 for incidence [81]
  • DENSE Trial: 13.4/1000 ICDR, 86% node negative

• Summary performance:
  • MR reduced the rate of interval cancers
    • 4.9 cancers per 1000 screening examinations to 0.8 cancers per 1000 screening examinations
  • Second round of MR screening reduced false-positive recalls
    • 80 recalls per 1000 screening examinations in the first round to 21 recalls per 1000 screening examinations in the second-round


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ABBREVIATED BREAST MRI
SUPPLEMENTAL SCREENING- AVG RISK, DENSE BREASTS

• Decreased scan time by performing a single contrast-enhanced T1-weighted acquisition, reviewing subtracted and maximum intensity projections

• Superior sensitivity (96% vs 39%) but reduced specificity (87% vs 97%) compared to incidence DBT screening

• ICDR 9.7/1000, 6.7/1000 invasive

• Biopsy rate was fourfold that associated with DBT (107 vs 29 biopsies)

• Lower positive predictive value 3 for biopsy (19% for MRI vs 35.5% for DBT)
BREAST MRI
SCREENING INDICATIONS

• Guidelines recommend breast MRI screening for:
  • Women at high risk of breast cancer (ACR, ACS and NCCN)
  • Women with a personal history of breast cancer and dense breasts (ACR)
  • Women with a personal history of breast cancer diagnosed by age 50 years (ACR)
BREAST MRI

BARRIERS

• High cost

• Very low rates of severe adverse events (0.17%) are observed (NSF, anaphylaxis)

• Gadolinium deposition
  • Intracranial deposition occurs in patients with many MR scans
  • No clear associated adverse effects have been identified
  • Deposition reduced with use of newer macrocyclic chelates

• Claustrophobia

• Comparatively high rate of false-positive findings
CONTRAST ENHANCED MAMMOGRAPHY
SUPPLEMENTAL SCREENING

• Technique
  • Injected iodinated contrast depicts cancers using mammography
  • Double the radiation of standard mammography, still considered not harmful

• Performance: Most data in cancer patients
  • CEM ICDR 8.6-13.1
  • Overall sensitivity of CEM mirrored that of MRI (97% each)
  • Overall specificity was 93.7% with a PPV3 of 29.4%
  • Specificity was higher with CEM (0.66; 95% CI, 0.59–0.71) than with MRI (0.52; 95% CI, 0.46–0.58) [94]
DUAL ENERGY SUBTRACTION

High energy image
Kv (45-49)>iodine K-edge

Low energy image
Kv (28-33)<iodine K-edge

Subtracted image
Isolates iodine only
CONTRAST ENHANCED MAMMOGRAPHY

BARRIERS

• Pooled rate of severe adverse reactions was 0.82% (95% CI, 0.64-1.05%), and staff should be trained to recognize reactions

• Lacks widespread direct biopsy capability for findings not visible on mammography or US, uncommonly resulting in the need for breast MRI followed by MRI-guided biopsy

• Lack of CPT code results in variable billing and reimbursement
  • Some centers use 2D mammography CPT code plus contrast add on charge

• May be perceived as less profitable than MRI
## SUMMARY OF SUPPLEMENTAL SCREENING FOR DENSE BREASTS

Summary of comparative impact of supplemental screening beyond 2D mammography for women with dense breasts and surrogate endpoint validation

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<td>Not yet evaluated</td>
</tr>
</tbody>
</table>

a: not evaluated; b: %; c: not yet evaluated; d: not yet evaluated; e: not yet evaluated; f: not yet evaluated; g: not yet evaluated; h: not yet evaluated; i: not yet evaluated; j: not yet evaluated; k: not yet evaluated; l: not yet evaluated; m: not yet evaluated; n: not yet evaluated; o: not yet evaluated; p: not yet evaluated.
QUESTIONS & DISCUSSION
THANK YOU FOR JOINING US IN THIS COURSE

Rochester, Minnesota
Phoenix, Arizona
Jacksonville, Florida
SLIDES MOVED TO END FOLLOW THIS SLIDE
# BREAST DENSITY PREVALENCE

Prevalence of breast density classifications among U.S. women aged 40-74 years

<table>
<thead>
<tr>
<th>Breast density classification</th>
<th>Prevalence (%)</th>
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</thead>
<tbody>
<tr>
<td>a</td>
<td>13.3</td>
</tr>
<tr>
<td>b</td>
<td>43.3</td>
</tr>
<tr>
<td>c</td>
<td>35.9</td>
</tr>
<tr>
<td>d</td>
<td>7.4</td>
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